Remarks

Claims 1-22 and 25-28 were pending in this application. Claim 1 is amended herein to incorporate the limitations of claim 7; claim 1 is also amended to correctly reference SEQ ID NO: 22. Additional support for the amendment of claim 1 can be found throughout the specification, such as, but not limited to, page 27 of the specification. Claims 3, 4 and 7 are canceled herein. Claim 2 is amended herein to incorporate the limitations of claim 3. Claims 5-6 are amended herein to correct form. Claims 8-18 are amended herein to correct dependency. Claims 20 and 27 are amended herein to correct form.

New claims 29-32 are added herein. Support for these new claims can be found throughout the specification, such as on pages 31-47.

Applicants believe no new matter is added herein. Reconsideration of the subject application is respectfully requested.

Claim Objections

Claim 22 is objected to for including the word "retroviral" twice. However, claim 22 is withdrawn from consideration, and does not include the word "retroviral." Applicants believe that there is a typographical error and that this objection should have been asserted against claim 20, which is amended herein to remove the second occurrence of the word "retroviral."

Rejections under 35 U.S.C. § 112

Claims 7-17 and 26 are rejected under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite in the recitation of SEQ ID NOs: 22-98. A substitute sequence listing is submitted herewith, and the claims are amended herein to refer only to SEQ ID NO: 22. Applicants submit that the submission of the substitute sequence listing and the amendment of the claims renders the rejection moot.

Claims 1-21 and 25-28 are rejected under 35 U.S.C. § 112, first paragraph, as failing to comply with the enablement requirement. Claims 3 and 7 are canceled herein, rendering the rejection moot as applied to these claims. Applicants respectfully disagree with this assertion as applied to claims 1-2, 4-6, 8-21 and 25-28 as amended.

The following Wands analysis is provided:

Nature of the invention: Applicants agree that the claims are drawn to a method of increasing an immune response to an opportunistic infection in an immunocompromised subject using an immunostimulatory D oligodeoxynucleotide (ODN). The ODN are 18 to 30 nucleotides in length and include a specified immunostimulatory motif (see claim 1). In some embodiments, the subject is immunocompromised as a result of an infection with an immunodeficiency virs (see claims 2, 4, 5, 6, 18-20 and 31-32) or as a result of chronic granulomatous disease (claim 30). In additional embodiments, the ODN has the nucleic acid sequence set forth as SEQ ID NO: 177 (claims 29 and 32).

State of the prior art: Applicants agree that the prior art describes D ODN, and discloses that administration of D ODN can lead to an immune response in a healthy (non-immunocompromised) individual. The response to CpG ODNs in normal (non-immunocompromised) subjects is known in the art (Verthelyi et al., J. Immunol. 166: 2372, 2001, copy submitted herewith as Exhibit A; Klinman et al., Vaccine 17: 19-25, 1999, of record).

The Office action references Klinman, 2004, page 3 as stating that HIV does not inactivate the immune system until late in the disease process (Applicants were unable to locate this reference. However, the same statement appears on page 4718 of Verthelyi et al., J. Immunol. 170: 4717-4723, 2003).

The claims clearly specify that the subject is *immunocompromised.* The time course of an HIV infection, and the effect on the immune system, is well known in the art (see "HIV" printed from Wikipedia, copy attached as Exhibit B). This article describes that Infection with HIV-1 is associated with a progressive decrease of the $CD4^+$ T cell count and an increase in viral load. The stage of infection can be determined by measuring the patient's $CD4^+$ T cell count, and the level of HIV in the blood. HIV infection has four stages: incubation period, acute infection, latency stage and AIDS. The initial incubation period upon infection is asymptomatic and usually lasts between two and four weeks. The second stage, acute infection, which lasts an

average of 28 days and can include symptoms such as fever, lymphadenopathy, pharyngitis, rash, myalgia, malaise, and mouth and esophageal sores. The latency stage, which occurs third, shows few or no symptoms and can last anywhere from two weeks to twenty years and beyond. AIDS, the fourth and final stage of HIV infection shows as symptoms of various opportunistic infections. It is only following the latency stage, during this fourth stage of AIDS, wherein the subject is immunocopromsed. Thus, it would be well known, and readily ascertainable to one of skill in the art when a subject infected with HIV is immunocompromised, as routine assays such as a CD4 count can be used to make this determination.

Breadth of the Claims: Claim 1 is amended herein to be directed to the treatment of any immunocompromised with an immunostimulatory D ODN of a specified sequence (SEQ ID NO: 22), wherein the D ODN is 18 to 30 nucleotides in length. Working examples are provided in the examples section. Specific ODN sequences (such as, but not limited to, SEQ ID NOs: 176-178) are provided (see page 45), contrary to the assertions raised in the Office action. Additional specific ODN sequences are provided in the sequence listing, and in the specification on pages 26-28. A declaration of Dr. Veritheyli is also provided herein documenting the results obtained using these ODN sequences in several model systems.

Working examples: Applicants agree that working examples include (1) the use of D ODN to produce an immune response to L. Major in SIV-infected monkeys, (2) the use of D ODN to produce an immune response to Listeria in mice with CGD disease and (3) *in vitro* studies documenting the production of an immune response in peripheral blood mononuclear cells isolated from HIV-infected human subjects. Thus, CpG ODNs have been documented to produce an immune response in immunocompromised subjects both in vivo and in vitro. Moreover, CpG ODN have been documented to produce an immune response in subject who became immunocompromised due to different etiologies (HIV infection, SIV infection, and CGD disease).

The statement on page 38 of the specification states that "...no single D or K motif is *optimally* stimulatory in all donors" [emphasis added]. Thus, D or K ODNs are still effective (qualitatively produce a resultn all donors, the different motifs can produced an increased or

decreased effect (quantitative difference) in different donors. The specification also states: "[h]owever, mixtures of ODNs were identified stat strongly stimulated PBMC from all human donors." Thus, to optimally stimulate (100% stimulation) in all donors at every administration, a mixture of CpG ODNs can be used. This use of multiple ODNs does not negate that fact that each D ODN is immunostimlatory and effective, albeit possibly at a lower quantitative level.

Submitted herewith is a Declaration of Dr. Daniela Verithelyi under 37 C.F.R. § 1.132 (herein after "the Declaration"). The Declaration provides data documentation that, using the methods and model systems disclosed in the specification, mixtures of D ODN could be used to induce immune responses to opportunistic infections in immunocompromised hosts, such as SIV infected macaques. These mixtures include more than one ODN with the nucleic acid set forth as SEQ ID NO: 22. Specifically, these mixtures include an ODN with the nucleic acid sequence set forth as SEQ ID NO: 177 (which is one embodiment of SEQ ID NO: 22), see also page 445 of the specification. In addition, the Declaration discloses that a single D ODN can be used to induce an immune response in peripheral blood mononuclear cells from immunocompromised human subjects with chronic granulomatous disease (CGD) *in vitro*, in SIV-treated macaques and in a mouse model of CGD. Thus, there are working examples provided in several model systems documenting that mixtures of D ODN, as well as individual D ODNs, can be used to increase an immune response in an immunocompromised host to an opportunistic infection.

Predictability of the art: The Office action alleges that there is "no way that an artisan could predict a successful cocktail of ODNs..." However, there is no factual evidence to support this assertion. Indeed, the Applicants have provided evidence documenting that both mixtures of D ODNs and individual D ODNs can be used to produce an immune response to an opportunistic infection.

The Office action asserts that the generation of an immune response to an opportunistic infection is unpredictable, as opportunistic infections have different initiating agents (such as bacteria, fungi, and viruses). Applicants do not deny that opportunistic infections result from infection of hosts from a variety of organisms. However, the administration of D ODNs has been shown to be effective in producing an immune response to a variety of opportunistic

infections, including Leishmainia, Listeria and hepatitis virus. Thus, as correctly recognized in the Office action, the inventors have documented that, surprisingly, D ODN broadly stimulate the immune response against a wide variety of pathological agents, including a bacteria, a protozoa, and a virus. Working examples documenting that an immune response can be produced in immunocompromised hosts against a broad range of organisms was provided in the specification. Additional experimental evidence is provided in the Declaration submitted herewith. The induced immune response includes increases in the number of dendritic cells, increased secretion of cytokines, and decreases in pathogen numbers and lesions. Given the guidance provided by the specification, and the number of working examples, there simply no factual basis for the allegation that D ODN could not be used to treat any type of opportunistic infection.

The Office action further alleges that immunocompromised subject include subjects with a large number of conditions, including AIDS and CGD. Applicants do not deny that a lot of agents/conditions can result in a host being immunocompromised. However, the specification discloses, and provides working examples documenting, that once the subject is immunocompromised, D ODNs will be effective in that producing an immune response to an opportunistic infection. The Applicants have provided working examples in PBMC from subjects who are immunocompromised as a result of an infection (cause be an HIV). Working examples were also provided documenting that D ODN can be used to produce an immune response to an opportunistic infection in PBMC from subjects who are immunocompromised as a result of a genetic condition, namely CGD. Thus, it is clear that the effect of D ODN in any immunocompromised subject would be predictable. Most certainly, as working example are provided using mixtures of D ODN including D35 (SEQ ID NO: 177) and D35 individually, the effect of this ODN (claims 27 and 29-31 are predictable). Specifically, the effect of D35 (SEQ ID NO: 177) has been documented both in subjects with CGD and in subjects infected with HIV.

Amount of experimentation necessary: The Office action alleges that there is a huge amount of experimentation necessary as (1) all ODNs and all mixtures must be tested to determine which is optimal; (2) whether each ODN would be effect in every immunocopromised host; and (3) whether a response to every opportunistic infection would be generated for every D

ODN. Applicants not that this rejection is seemingly issued only against claim 1, as the dependent claims recite specific disease conditions (for example, claims 2-6 and 18-20) which are limited to HIV infections) or specific ODNs (for example claims 27, 29 and 32). No factual basis has been provided for the assertion in the Office action that the amount of experimentation required is undue. Indeed, the Applicant has provided evidence that (1) several D ODNs, which have nucleic acid sequence specified in claim 1, either individually or in mixtures can be used to produce an immune response to an opportunisitic infection in an immunocompromised host; (2) these D ODNs were effective in individuals with different biological basis for the immunocompromised state, including a genetic condition and an infection with an immunodeficiency virus, and (3) immune response can be produced to more than one type of opportunistic infections, including bacterial, viral and protozoan infections. Clearly the synthesis of D ODNs is routine for one of skill in the art. In addition, tests to ascertain if an immune response is produced (such as by counting the number of CD4 cells) are clearly routine to one of skill in the art. Thus, there is ample guidance provided to practice the claimed methods, and several working examples. Any experimentation required to practice the claimed methods would simply be routine.

Reconsideration and withdrawal of the rejection are respectfully requested.

Conclusion

Applicants believe the pending claims are in condition for allowance, which action is requested. If for any reason the rejection under 35 U.S.C. § 112, first paragraph is maintained, or if any new rejections are asserted, the Examiner is formally requested to contact the undersigned prior to issuance of the next Office action, in order to arrange a telephonic interview. It is believed that a brief discussion of the merits of the present application may expedite prosecution. This request is being submitted under MPEP §713.01, which indicates that an interview may be arranged in advance by a written request.

Respectfully submitted,

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